IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Art Unit: 1644
JENSENIUS, et al.	)	Examiner: SAUNDERS, David
Serial No.: 09/874,238	)	Washington, D.C.
Filed: June 4, 2001	)	November 24, 2004
For: MASP-2, A COMPLEMENT-FIXING ENZYME, AND USES FOR IT	)	Docket No.: JENSENIUS=3B
	)	Confirmation No.: 6910

THIRD 37 CFR 1.132 DECLARATION OF JENS CHRISTIAN JENSENIUS

S i r :

1. I am one of the originally named inventors of the above-identified patent application.

2. I have read and understand the above-mentioned patent application, including the claims. I have reviewed the amendment filed October 5, 2004, and my comments are directed to the claims as they would be amended if that amendment were entered.

3. The protein now designated bovine MASP-2 was isolated and identified in Aarhus by Steffen Thiel (ST) and Jens Chr. Jensenius (JCJ) through its reaction with a chicken antibody. Said antibody was raised by ST and JCJ by immunizing chickens against a preparation of bovine plasma lectins and lectin-associated proteins.

A lectin preparation was purified from human plasma and a protein, later termed human MASP-2, was identified from said fraction by Western blotting using the chicken antibody described above. The N-terminal amino acids of this protein of 52 kDa by SDS-PAGE was sequenced by Anthony C. Willis (ACW) from blots on PVDF membranes provided by ST and JCJ.

An antibody (anti-N'-MASP-2) raised against a synthetic peptide representing the identified N-terminal 19 amino acids was then prepared by ST and JCJ. This antibody was shown to react with the 52 kDa protein as well as with proteins of 76 kDa and

20 kDa. The N-terminal of the 76 kDa protein showed sequence similarity to a previously identified protein, termed MASP. ST and JCJ showed that upon activation the 76 kDa protein was generating the 52 kDa fragment.

The protein identified by the antibodies described above was found to be associated with mannan-binding lectin and was found to be able to activate the complement factor C4.

ST and JCJ deduced that the new protein could be a protein with similarity to the protein previously named "MASP" (now termed MASP-1) and thus suggested the name MASP-2 for the new protein.

Further, ACW sequenced some internal peptides of the 52 kDa protein, and also the 20 kDa form. These sequencing efforts established the 52 kDa protein as being related to MASP-1, C1r and C1s. The sequencing also established the 20 kDa protein as being a truncated form of the 52 kDa protein.

The Aarhus group, including research students Søren Hansen and Steen B. Laursen, showed the 52 kDa protein as well as the truncated form to be associated with mannan-binding lectin. Uffe Holmskov (UF), Odense, was involved in this finding through ongoing discussions. However, Hansen, Laursen and Holmskov did not play a role in the sequencing of human MASP-2 or the preparation of anti-human MASP-2 antibody.

In Aarhus, graduate student Thomas Vorup Jensen (TVJ) generated by RT-PCR a 300 bp cDNA fragment from liver RNA using oligonucleotides deduced from the peptide sequences. The amino acid sequence deduced from the 300 bp oligonucleotide encompassed the peptides used for constructing the oligonucleotides as well as another of the sequenced peptides. The derived sequence further emphasized the similarity of the new protein to MASP (MASP-1) and also the relationship to C1r and C1s.

TVJ, working in Kenneth B. M. Reid's (KBMR) laboratory in Oxford with guidance of KBMR and Paul Eggleton (PE) used the 300

bp as probe for cloning cDNA from liver libraries and isolated a 1.8 kb clone. The sequence revealed the presence of the serine protease domain, although the C-terminal part of this was missing. Also missing (compared to the later obtained full length clone) was the 2nd C1r/s domain.

Wilhelm Schwaeble (WS) heard of the project and offered his help with isolating and sequencing further clones. The aim of this was to establish the full sequence of the mRNA and thereby also the deduced amino acid sequence. This work would also allow for the synthesis by recombinant technique of the recombinant protein. The synthesis of the recombinant protein as well as of MASP-1 and possibly also MBL was allocated to TVJ to be part of his PhD project aimed at studying the structure and function of the MBL/MASP complex. This work was designed to be carried out in collaboration with KBMR and Robert B. Sim (RBS) in Oxford as well as at the Aarhus laboratory.

With the use of the 300 bp TR-PCR generated probe, the cloning and sequencing was successfully carried out in WS's laboratory in Leicester, largely by graduate student Cordula Stover (CS). Three different cDNA clones were sequenced. One (A) represents the full length was found to encode a protein of 622 amino acids showing about 40% sequence identify to C1r, C1s and MASP-1. Another clone (C) represented the N-terminal part of clone A with additional four amino acids not found in A. The size of C (ORF of 540 bp) agrees with it representing mRNA encoding the truncated form of MASP-2. The third clone (B) has a 5' end almost identical to C but in addition an ORF of 558 bp with no similarity to A.

Working as a graduate student under guidance of Wilhelm Schwaeble, CS cloned and sequenced cDNA sequences encoding i.a. full-length MASP-2. This was accomplished with the aid of a 300 bp cDNA fragment generated by RT-PCR from liver. Said fragment was cloned by the graduate student Thomas Vorup Jensen under

guidance of Steffen Thiel and Jens Chr. Jensenius. three different cDNA clones were sequenced. One (A) represents the full length was found to encode a protein of 622 amino acids showing about 40% sequence identity to C1r, C1s and MASP-1. Another clone (C) represented the N-terminal part of clone A with additional four amino acids not found in A. The size of C (ORF of 540 bp) agrees with it representing mRNA encoding the truncated form of MASP-2. The third clone (B) has a 5' end almost identical to C but in addition an ORF of 558 bp with no similarity to A.

The individuals involved with DNA cloning and sequencing (TVJ, KBMR, PE, WS, RBS, CS) were not involved in the original sequencing of the N-terminal of human MASP-2, nor in the preparation of any anti-MASP-2 antibodies.

4. I am familiar with the publication Thiel et al., "A second serine protease associated with Mannan-binding lectins that activates complement", Nature 386:506-10 (April 3, 1997). I have been informed that the Examiner has cited this publication as evidence of inventive contributions to the claimed subject matter by the omitted coauthors (Vorup-Jensen, Schwaeble, Laursen, Poulsen, Willis, Eggleton, Hansen, Holmskov, Reid and Stover).

5. I previously stated the opinion that none of the omitted co-authors were inventors.

6. On September 30, 2004, I signed a 37 CFR 1.63 declaration naming Jensenius, Thiel and Willis as joint inventors, with the understanding that the declaration was being filed in support of a petition to correct inventorship by adding Willis as a joint inventor. This, in turn, was in response to the Examiner's argument that the first antibody which specifically bound MASP-2 was the anti-N-terminal peptide, and that Willis provided the necessary peptide sequence. I have deferred to the Examiner's expert opinion on inventorship.

7. The Examiner has argued that Vorup-Jensen, Reid, Eggleton, Schwaeble, Sim and Stover made inventive contributions to claim 40 because of their contributions to the determination of SEQ ID NO:2. Since the October 5, 2004 amendment proposed cancellation of claims 40 and 42, it is my opinion that no one, other than Jensenius, Thiel, and Willis, made an inventive contribution to the invention defined by the claims as proposed to be amended on October 5, 2004. Hence, I don't believe that Vorup-Jensen, Reid, Eggleton, Schwaeble, Sim or Stover or indeed, any individual other than Jensenius, Thiel and Willis should be named as a joint inventor herein.

8. I consider the 20 kDa polypeptide, a truncated form, to be within the meaning of "a human MASP-2". See P4, L24-26. Thus, an antibody which binds both the 20 kDa and 52 kDa polypeptides still can be said to specifically bind human MASP-2.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Jens Christian Jensenius — Dec 1 2004

Jens Christian Jensenius — Date

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SECOND 37 CFR 1.132 DECLARATION OF STEFFEN THIEL

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Steffen Thiel

1. december - 2004
Date

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